of the isolated and purified peptide comprising a leucine positioned two peptide bonds away from a tyrosine-arginine pair, and] wherein the peptide from which the specific binding protein is raised to consists of from 5 to 71 amino acids.

37. (Amended) A recombinant specific binding molecule which specifically binds to the defined epitope bound by the binding protein of claim 36.

43. (Amended) A recombinant specific binding molecule which specifically binds to the defined epitope bound by the antibody of claim 41.

**In the Sequence Listing:**

Please replace Sequence Listing with an amended Sequence Listing and computer readable form attached herewith. The Sequence Listing has been amended to include peptide sequences contained within figures 6 and 7.

**REMARKS**

Regarding ¶ 4 of the Office Action, the Examiner has stated that the art search has been expanded to include the peptides CPEGYRYNLKSKSC, SPEGYRYNLKSKSSE, LREVEYRYALQMEQLN. The Applicants respectfully submit that these peptides are not similar to the peptides claimed in the present invention, in view of the amendment to claims as stated above.

Regarding ¶¶ 5 and 6 of the Office Action, the Examiner has rejected claims 6-11, 15-17, 21, 23, 27-30, 34-37 and 43 under U.S.C. § 112, arguing that the specification does not provide enablement for the composition or method further comprising a specific binding protein which specifically binds a peptide comprising: A) a leucine positioned two peptide bonds away from a tyrosine-arginine pair; B) comprising SEQ ID NOS:1-3; C) wherein said peptide consists of from

5 to 71 amino acids; D) a leucine positioned two peptide bonds away from a tyrosine-arginine pair; E) which comprises SEQ ID NO:5 or a conservative variant thereof; and F) a leucine positioned two peptide bonds away from a tyrosine-arginine pair. The Examiner asserts that the specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Applicants respectfully traverse all six of these rejections.

Regarding points A, B, D and F, the Applicants submit that they have provided in the specification data that support this invention. Specifically, the specification describes data from phage display experiments. Phage display technology allows the panning of $2 \times 10^9$ randomized 7-mer peptides to map the epitopes of antibodies. The specification provides that a 7 amino acid peptide (SEQ ID NO:4) as well as several other 7-mer peptides (see enclosed declaration from Greg Francoeur) inhibited monoclonal antibody 8H.8 from binding to either native or recombinant canine IgE (pg. 28, lines 10-13). In addition, several other peptides were synthesized, and found that the Leu-Xaa-Xaa-Tyr-Arg motif was common amongst the peptides that bound the 8H.8 antibody (see pg. 28, lines 14-18 and figures 12 and 16) as well as the native canine IgE exon 3 sequence. Human IgE, which differs from the above motif by one amino acid (Tyr to Arg substitution; see table 2 on page 36), does not bind to the 8H.8 antibody, as well as feline IgE and canine IgE with a single amino acid substitution to resemble human and feline IgE. From this data, it can be concluded that not only is the motif critical for achieving binding of the 8H.8 antibody, but that the two amino acids between the critical groups are not important for 8H.8 binding. The Applicants respectfully submit that the specification provides sufficient enablement of the rejected claims and does not require undue experimentation.

Regarding points C and E, the Applicants submit that the specification discloses that

conservative variants of amino acid sequences "include amino acid substitutions or deletions that do not substantially affect the character of the variant polypeptide relative to the starting peptide" (see pg. 15, lines 10-13). The specification also contains an example of a polypeptide whose character is not substantially affected as "substitutions or deletions which do not preclude specific binding of the variant peptide to a specific binding partner of the starting peptide" (see pg. 15, lines 13-16). Thus, the specification teaches that conservative variants of amino acid sequences would be variants which could, despite the substitution or deletion of amino acids, bind to the specific binding partner of the starting peptide.

The specification gives one such example of a conservative variant of amino acid sequence which could bind to the specific binding partner of the starting protein. The antibody 8H.8 was produced by immunization with a 71 polypeptide fragment of exon 3. 8H.8 was then used in phage display experiments to determine the epitope of 8H.8. The epitope was a 7–mer peptide (SEQ ID NO: 9) that contained 6 amino acids common in form and/or spacing to the C-terminal region of exon 3. The Leu-Xaa-Xaa-Tyr-Arg motif was deduced from the phage display experiments, and a conservative variant of the phage display peptide, SEQ ID NO: 10 was synthesized and found to also bind to the 8H.8 antibody with high affinity. Therefore, amino acids of a peptide could be substituted (a comparison of SEQ ID NOS: 9 and 10 reveal that 4 of 7 amino acids have been substituted) with similar affinity as the starting peptide. In addition, peptides which were dissimilar in length to the 71 amino acid immunogen were also capable of binding to the 8H.8 antibody. This indicates that non-critical amino acids could be substituted or added (up to 71 amino acids in length) without significant changes in antibody binding. This is supported in the literature, where the critical region for antibody binding of peptides has been found to be highly ordered and structured. Substitutions within this region (i.e. Leu-Xaa-Xaa-

Tyr-Arg) can ablate antibody binding. In contrast, the region outside of antibody binding is highly disordered, and substitutions which retain secondary structure characteristics are allowed (Exhibit A: Stanfield and Wilson, "Protein-peptide interactions", Current Opinion in Structural Biology, 1995, pg. 104).

The Applicants also contend that the claimed invention teaches the importance of the Leu and Tyr-Arg groups as well as the spacing. Experiments disclosed in the specification have shown that one amino acid change in the peptide can ablate antibody binding (pg. 55, lines 1-7). That all of the amino acids outside of this critical sequence have been changed (see above) teaches that substitutions of the surrounding amino acids can be made without decreases in antibody affinity. Therefore, the Applicants submit that the rejection should be withdrawn because the specification provides guidance as to which amino acids can be changed while peptide activity is retained.

Even if one assumes that the total number of amino acids that can be changed is large, the Applicants believe that it is well known in the art that amino acids can be conservatively substituted without significantly changing the structure or binding characteristics of a peptide or protein. The Dayhoff Minimum Mutation Matrix, a weighted scale constructed for the purpose of measuring the similarity between two different proteins, weighs the amino acid change between two proteins and determines if the change is conservative or substantial (Exhibit B: Dayhoff, "Atlas of protein sequence and structure", 1968, Chapter 4). By using matrices such as the Dayhoff matrix, an investigator can compare two amino acids and obtain a "similarity" value for the pair. Doolittle presents an elegant table which merges two different matrices, allowing an investigator 2 different methods to analyze the similarity in an amino acid substitution (Exhibit C: Doolittle, "Of Urfs and Orfs, A primer on how to analyze derived amino acid sequences",

1987, Table III, pg. 18). For example, both matrices agree that a Glu to Asp, Val to Ile, Ser to Thr, Arg to Lys and Gln to Asn are conservative changes (supra, page 17). Non-conservative changes would be a Asp to Trp, Phe to Glu, Lys to Tyr, and many others listed in the table (supra, Table III, pg. 18). Matrices also have been constructed for observing the replaceability of amino acid residues in peptide epitopes for antibody binding (Exhibit D: Geysen et al, "Cognitive Features of Continuous Antigenic Determinants", 1989, Table I, pg. 24). Within an epitope defined on a short (5-8 residues) peptide, non-critical amino acids could be substituted without significantly changing the binding affinity from the starting peptide. It was found that replaceability of an amino acid was successful if the change was conservative (supra, pg. 22-23).

Conversely, as cited by the Examiner in Lederman et al (1991) and Abaza et al (1992), non-conservative substitutions or deletions, regardless of whether they are within the epitope or outside of the binding region, result in significant changes in the peptides binding and structural characteristics. In addition, the references can be distinguished from the present invention because they are concerned with proteins, not synthetic peptides. The proteins are capable of forming tertiary structures, which complicates the issue of antigenicity and epitope recognition. Peptides do not form tertiary structures, and for the most part, have epitopes that comprise linear, continuous stretches of amino acids (Stanfield and Wilson, supra, pg. 104). Thus, the specification, in light of the well-known prior art regarding amino acid characteristics and peptide-antibody interactions, teaches a very limited amount of substitutions or deletions that could be performed without decreasing or eliminating the binding affinity as compared to the starting peptide. These types of experiments do not require undue experimentation in order to practice the invention as claimed.

In light of the foregoing, reconsideration of the six rejections under U.S.C. § 112 is respectfully requested.

Regarding ¶ 7, the Examiner rejected claims 1-2, 6-10, 17, 23, 27-30, 34-37, and 43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not adequately described in the specification. The Examiner objects to the lack of definition regarding specific binding proteins other than antibodies.

The Applicants respectfully traverse this rejection. The specification provides a definition of specific binding proteins (molecules) as "A molecule (protein) that exhibits specific binding to its corresponding binding partner to form a specific binding pair" (pg. 17, lines 16-18). Moreover, the specification provides examples of specific binding proteins (molecules) as "monoclonal and polyclonal antibodies, antigen-binding fragments of these antibodies, hybrid antibodies, single-chain antibodies, and recombinant molecules capable of specific binding to a ligand" (pg. 17, lines 18-22). The Applicants have also defined the term "recombinant specific binding proteins" as artificial hybrid molecules (pg. 17, lines 6-9) which are capable of specific binding to a ligand" and "exhibits specific binding to its corresponding binding partner to form a specific binding pair" (page 17, lines 16-22). The Applicants submit that the specification provides sufficient definition of a specific binding protein and provides examples as to what a specific binding protein is. In view of these comments, reconsideration of the rejection is respectfully requested.

Regarding ¶ 8 of the Office Action, the Examiner rejected claims 41 and 42 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described adequately in the specification. The Examiner objects to the lack of a biological deposit of the monoclonal

antibody 8H.8 in order to make it readily available to the public or obtainable by a repeatable method set forth in the specification.

The Applicants respectfully traverse this rejection. It is well established in case law that claims of this type do not require a deposit to satisfy 35 U.S.C. §112. See e.g. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). The Applicants submit here that the prior art regarding monoclonal antibody production was well known at the time of application. The Applicants also submit that the specification contains the information necessary for producing the 8H.8 antibody, most importantly, the antigen that was used to produce the monoclonal antibodies (see pg. 24, lines 13-17). The Applicants therefore submit that because no undue experimentation is necessary to produce the 8H.8 antibody, there is no need for a biological deposit. In view of these comments, reconsideration of the rejection is respectfully requested.

Regarding ¶¶ 8 and 9 of the Office Action, the Examiner has rejected Claims 7-8, 11, 15-17, 21-23, 27-30, and 34-37 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner specifically lists 5 points, labeled A-E, which he objects to.

Regarding point A in ¶ 9 of the Office Action, the Examiner objects to the use of the word "blank" in Claim 7 since it renders the claim ambiguous and indefinite. The Examiner suggests instead the use of "Xaa" to denote "any amino acid." Applicants have adopted the use of equivalent terminology suggested by the Examiner.

Regarding point B in ¶ 9 of the Office Action, the Examiner objects in claims 11-12, 21, 27-28, and 34-35, to the recitation of the term "an antibody...which is raised to...a peptide" since it renders the claims ambiguous and indefinite. Applicants disagree as this usage is common to those skilled in the art. The term "which is raised to" refers to the fact that antibodies are well

known to be generated (raised) in response to the presence of a particular antigen. Since the antigen in this case is well characterized, the terminology "is raised to" is not vague or ambiguous in context.

Regarding point C in ¶ 9 of the Office Action, the Examiner states that in claim 11, the phrase "antibody of claim 9" has no antecedent basis. Applicants respectfully disagree. Claim 9 reads: "A specific binding protein of Claim 6 which is an antibody," therefore, claim 9 is a claim to an antibody and claim 11 further defines the antibody by describing the epitope it was raised to.

Regarding point D in ¶ 9 of the Office Action, the Examiner objects to the recitation of the term "recombinant binding molecule" in claims 17, 23, 30, 37 and 43 since it renders the claims ambiguous and indefinite. The term "recombinant DNA molecule" is defined in the specification as "A hybrid DNA sequence comprising at least two nucleotide sequences, the first sequence not normally being found together in nature with the second" (page 17, lines 6-9). The specification further defines a "recombinant specific binding molecule" as recombinant molecules which are capable of specific binding to a ligand" and "a molecule that exhibits specific binding to its corresponding binding partner to form a specific binding pair" (page 17, lines 16-22). Taken together, the specification provides that the term "recombinant specific binding molecule" are artificial hybrids that are capable of specifically binding to a ligand or corresponding binding partner. The Applicants have amended the claims to substitute the term "recombinant specific binding molecule." This terminology has support in the specification (see e.g. pg. 17, lines 6-9 and lines 16-22).

Regarding point E in ¶ 9 of the Office Action, the Examiner objects to the recitation of the laboratory designation "8H.8" since it renders the claim ambiguous and indefinite. The

Applicants disagree that this term is ambiguous or indefinite because the epitope from which the antibody was made is well characterized. An antibody raised to that epitope would be an equivalent to 8H.8. Therefore, the term is sufficiently specific. Moreover, an applicant is entitled to be his own lexicographer.

In light of the foregoing comments, reconsideration and withdrawal of the rejections based on 35 U.S.C. § 112 is respectfully requested.

Regarding ¶¶ 11 and 12 of the Office Action, the Examiner has rejected claims 1-2 and 6-11 under 35 U.S.C. § 102 (b) as being clearly anticipated by WO 95/31728. The Examiner states that WO 95/31728 teaches a specific binding protein (monoclonal antibody) which specifically binds to a purified peptide (pg. 6, lines 16 and 27) comprising a leucine positioned two peptide bonds away from a tyrosine-arginine pair (including SEQ ID NOS:1-3) wherein one of the intervening amino acids comprises an aromatic ring.

This rejection is respectfully traversed. The Applicants submit that although Claims 6-11 state a peptide "comprising a leucine positioned two peptide bonds away from a tyrosine-arginine pair," the specification actually provides for a leucine positioned two **amino acids** away from a tyrosine-arginine pair. This is apparent from the examples given in Claim 7, as well as page 10, lines 16-23. These examples provide for 3 peptides, namely SEQ ID NO: 1 Leu-**Xaa-Xaa**-Tyr-Arg, SEQ ID NO: 2 Tyr-Arg-**Xaa-Xaa**-Leu, and SEQ ID NO: 3 Leu-**Xaa-Xaa**-Tyr-Arg-**Xaa-Xaa**-Leu. The applicants submit that the statement in Claims 6 and 11 was an error and should read "An isolated and purified peptide comprising a leucine positioned two amino acids away from a tyrosine arginine-pair" based on the sequences referred to in both the claims and specifications. Amended claims 6 and 11 overcome the rejection to the peptide on pg. 6, line 16 in WO 95/31728, which is for a peptide **one** amino acid away from a tyrosine-arginine pair. The

sequence disclosed on pg. 6, line 27 in WO 95/31728, is a peptide that is two amino acids away from a tyrosine-arginine pair. Applicants have amended claims 6 and 7 to overcome Examiner's rejection. In view of these amendments, reconsideration and withdrawal of this rejection is respectfully requested.

Regarding ¶ 13 in the Office Action, the Examiner has rejected claims 1-2 and 6-11 under U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5, 321,123. The Examiner states that the '123 patent teaches a specific binding protein (monoclonal antibody) which specifically binds to a purified peptide comprising a leucine positioned two peptide bonds away from a tyrosine-arginine pair (including SEQ ID NOS:1-3) wherein one of the intervening amino acids comprises an aromatic ring. Amended claims 6 and 7 do not contain the sequence Arg-Tyr-Xaa-Xaa-Leu, where Xaa is any amino acid, which is disclosed in the '123 patent. In view of these amendments, reconsideration and withdrawal of the rejection is respectfully requested.

Regarding ¶ 14 and 15 in the Office Action, the Examiner has rejected claims 1 and 2 under 35 U.S.C. § 103(a) as being unpatentable over Chang U.S. Patent No. 5,428,133 (1995) in view of DeBoer et al. (1993). The Examiner states that the '133 patent teaches a specific binding protein which specifically binds free IgE but does not bind to IgE bound to a receptor on mast cells, said specific binding protein being useful for the treatment of IgE mediated allergic diseases. The Examiner also states that, in light of DeBoer et al. which teaches a canine specific anti-IgE antibody and that IgE mediated allergic diseases pose a significant health problem in dogs, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce an anti-IgE specific binding protein for the treatment of allergic disease, as taught by the Chang '133 patent, said binding further being canine specific, as taught by DeBoer et al. One of ordinary skill in the art would have been motivated to make said canine

specific binding protein because IgE mediated allergic diseases pose a significant health problem in dogs, as taught by DeBoer et al.

The Applicants respectfully traverse this rejection. The Applicants have disclosed in the specification that the state of the art of canine allergy treatment at the time of the application was undeveloped (pgs. 3-4). The extent of IgEs role in allergic reactions was unknown since, unlike humans, IgE was not found to be elevated during acute reactions (pg. 3 line 30-pg. 4, line 4). In addition, although a canine IgE antibody was available, as cited in DeBoer et al. (1993), it was not obvious as to whether it would be beneficial in allergy treatments since antibodies which bind to IgE bound to the surface of mast cells actually trigger histamine release and manifest allergic symptoms ('133 patent, column 4, lines 7-9). Therefore, the Applicants submit that substantial, non-obvious experimentation was necessary in order to: 1) Prove that treatments directed towards decreasing IgE levels would benefit canine allergy patients because IgE levels are not increased during allergic reactions, indicating that IgE may not play a large role in the allergy cascade; and 2) If anti-IgE treatments are beneficial, what type of molecule would prove beneficial since anti-IgE antibodies can themselves trigger the allergy cascade. The Applicants submit that they have, with novel experimentation, answered both non-obvious questions and produced the invention described herein.

The claimed invention is also non-obvious in light of the Chang '133 patent because the '133 patent teaches away from the present invention. The '133 patent teaches an antibody which binds free IgE but does not bind to IgE bound to a receptor on mast cells. The antibody disclosed in the present invention provides that although the antibody does not bind to IgE bound to a receptor on mast cells, it also does not bind free, soluble IgE (see pgs. 24-26). In ELISA experiments performed with soluble native canine IgE, soluble IgE was not able to inhibit the

binding of monoclonal antibody to labeled bound canine IgE (pg. 25 line 14- pg. 26 line 2). This suggests that antibody does not bind to soluble (free) canine IgE, most likely due to masking of the epitope in the "free" phase (pg. 27, lines 17-29). This characteristic distinguishes the claimed antibody from the antibody disclosed in the '133 patent, and exhibits that the '133 patent teaches away from the present invention.

The Applicants believe that this case is in condition for allowance and respectfully request prompt favorable consideration of this Amendment and Response to Office Action.

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Respectfully submitted,

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